REMARKS/ARGUMENT

In order to expedite allowance of this application, claims 1 and 5 have been combined and a corresponding change has been made in claim 9. In addition, a series of new dependent claims have been added, all of which find basis in the previously pending claims.

The Examiner's indication that claim 8 would be allowable in independent form has been noted with appreciation. It is respectfully that new claims 12, 13 and 15 also fall into this category.

While the rejection set forth in the claim rejection paragraphs 3A and 3B are clearly moot in light of the foregoing amendment, it would appear that a rejection under 35 U.S.C. 103 over Hanisch in view of Hershenson and Cymbalista remains to be addressed. It is respectfully submitted that the proposed combination of references does not render the claimed invention obvious.

On May 23, 2002, the BPAI vacated the appeal and remanded this case to the Examiner. The remarks by the Board focused on the claimed interferon-beta dosage amount but did not reflect on many of the observations which are being made below.

The claimed invention relates to a liquid pharmaceutical formulation consisting of from about 0.6 to 24 MIU/ml interferon-beta, mannitol, an acetate buffer at a pH between 3.0 and 4.0, and optionally, albumin. A container hermetically sealed in sterile condition as well as a process for formation of the liquid pharmaceutical formulation are also claimed.

The Hanisch patent teaches a stable pharmaceutical composition containing a therapeutically effective amount of recombinant interferon-beta or interleukin-2 dissolved in a non-toxic, inert, therapeutically compatible aqueous carrier. Two distinct formulations

are described. One is a formulation produced by diafiltration or desalting at a high pH of about 8.5 - 10 followed by adjusting the pH to about 2 - 4 with an acidic agent. The resulting low pH solution does not require a stabilizer, but may optionally contain a carbohydrate stabilizer such as dextrose or mannitol (column 5, line 6-23). What is relevant to the claimed invention, therefore, is the description of a pH 2 - 4 liquid formulation containing interferon-beta and optionally a stabilizer which possibly is mannitol.

The second formulation involves adding an appropriate base to a low pH formulation to adjust the pH to about 6.8 - 7.8 but this formulation is less relevant with respect to the instant claims.

Hanisch does contain some reference to the possible use of human serum albumin as a stabilizer. However, Hanisch teaches that the "type of stabilizer employed and the concentration thereof will depend mainly on the pH method and formulation employed and on the protein." See column 9, lines 37 - 39. Albumin is preferred for high pH formulations or formulations treated at low pH where the protein is interleukin-2. *Id.* at lines 39 - 43. "However, for low pH formulations using [interferon beta], PPF [human plasma protein fraction] is preferred. *Id.* at lines 43-44. The preference for PPF over albumin (HSA) is reinforced by Example 3 which shows that a low concentration of PPF provided a very clear interferon-beta material while a high concentration of albumin was required to do the same. Note further that while Hanisch has several references to buffers in the text, such buffers are used during the recovery of the recombinant protein from its production broth. There is no clear disclosure in this reference of a liquid pharmaceutical composition containing interferon-beta, mannitol and a buffer, and optionally albumin.

The Hershenson reference has been relied on, *inter alia*, to show the quantity of interferon-beta. The reference does, of course, contain the disclosures concerning the normal dosage formulation to which the Examiner and the Board have referenced. It should be noted, however, that Hershenson teaches that to have a stable composition, one must use an effective amount of glycerol or of polyethylene glycol polymers as a stabilizer. The reference also teaches the use of a buffer, albeit not an acetate buffer, to maintain the formulation at a pH in the range of about 2 to about 4. Hershenson further indicates that the compositions can comprise an additional stabilizing agent and two of the twelve possibilities are mannitol and albumin. This reference thus teaches that where there is a liquid formulation containing a normal dosage amount of interferon-beta mannitol and a buffer to maintain the pH between 2 and 4 and, possibly, mannitol and/or albumin, the formulation must also contain either glycerol or polyethylene glycol polymers. The claims under consideration here exclude both glycerol or polyethylene glycol polymers.

The Cymbalista patent has been cited to show the use of an acetate buffer. It does have such a disclosure, but only in connection with a liquid formulation which contains polyvinyl pyrrolidone (PVP) as a stabilizer. There is no teaching or suggestion that the acetate buffer can be used in the absence of the PVP.

Hershenson teaches that a buffer such as a phosphate buffer can be used for an interferon-beta formulation provided that either glycerol or polyethylene glycol is present. The present invention does not use either glycerol or polyethylene glycol. Cymbalista teaches that an acetate buffer can be used but only if PVP is used as a stabilizer. The present invention does not use PVP. Hanisch teaches that the type of stabilizer (and its concentration) is dependent on the pH (a buffer controls the pH), as well as the formulation and protein employed. It is respectfully submitted that the Hanisch teaching

means that one cannot extract a feature from another reference merely because it is disclosed in that other reference. There is no basis in the present record for making those selections from the secondary references which are necessary to reproduce the claimed invention and combine them with features said to be optional by Hanisch.

While various bits and pieces of the claimed invention can be found in these three references, nothing in any of them teach or suggest the selection and combination of the particular materials recited in the instant claims. To make the appropriate selections requires the use of hindsight.

The foregoing considerations are reinforced by the Declaration of Dr. Esposito, which is already of record.

The teachings of the Hanisch reference with respect to sensitivity of the formulation to its ingredients are also confirmed by the data in the application. Thus, Table 1 shows that the formulation loses 27% of its potency after 1 day during accelerated (50° C) testing in a citrate buffer at pH 3 (and virtually all activity at 30 days), loses 80% at pH 4 and essentially loses 100% at pH 5 or 6. Table 3 shows essentially a total loss of activity on the 7th day of accelerated testing using an ascorbic buffer at pH 3 or 4 and a loss of almost 40% in a succinate buffer pH 3 or 4. Table 2 shows that in an acetate buffer at pH 5 and 6, there was a loss of activity of 43% to 55% after 1 day of such accelerated testing. Surprisingly, and in contract to these results, using an acetate buffer at pH 3 and 4 resulted in a loss of activity after 1 day of accelerated testing of only 28% or less while retaining 30% or more activity at 30 days.

Nothing in the prior art teaches that the combination of interferon-beta, mannitol, and an acetate buffer at a pH between 3.0 and 4.0, and optionally albumin, will give such outstanding results.

In light of all of the foregoing, it is respectfully submitted that this application is now in condition to be allowed and the early issuance of a Notice of Allowance is respectfully solicited.

Respectfully submitted,

Edward A. Meilman
Registration No.: 24,735
DICKSTEIN SHAPIRO MORIN & OSHINSKY, LLP
1177 Avenue of the Americas
New York, New York 10036
Telephone: (212) 835-1400

EAM:hg

APPENDIX A
Version With Markings To Show Changes Made
37 C.F.R. § 1.121(b)(1)(iii) AND (c)(1)(ii)

CLAIMS:

1. A liquid pharmaceutical formulation consisting of from about 0.6 to 24 MIU/ml of interferon-beta, mannitol, [a] an acetate buffer at a pH between 3.0 and 4.0 and, optionally, albumin.

3. A liquid pharmaceutical formulation according to claim[s] 1, in which interferon-beta is recombinant.

9. A process for the preparation of a liquid pharmaceutical formulation according to claim 1, comprising combining interferon-beta with mannitol, [a] an acetate buffer at a pH between 3.0 and 4.0 and, optionally, albumin.

APPENDIX B
"Clean" Version Without Amended/New Indications
37 C.F.R. § 1.121(b)(1)(iii) AND (c)(3)

CLAIMS:

1. A liquid pharmaceutical formulation consisting of from about 0.6 to 24 MIU/ml of interferon-beta, mannitol, an acetate buffer at a pH between 3.0 and 4.0 and, optionally, albumin.

3. A liquid pharmaceutical formulation according to claim 1, in which interferon-beta is recombinant.

4. A liquid pharmaceutical formulation according to claim 1, in which interferon-beta is in a quantity between 0.6 and 1 MIU/ml.

6. A liquid pharmaceutical formulation according to claim 4, in which the buffer solution has a concentration of 0.01 M.

7. A liquid pharmaceutical formulation according to claim 1, which also comprises human albumin.

8. A liquid pharmaceutical formulation according to claim 1, comprising 1 MIU/ml of interferon-beta, 54.6 mg/ml of mannitol, 0.5 mg/ml of albumin in a solution of 0.01 M acetate buffer at pH 3.5.

9. A process for the preparation of a liquid pharmaceutical formulation according to claim 1, comprising combining interferon-beta with mannitol, an acetate buffer at a pH between 3.0 and 4.0 and, optionally, albumin.

10. A container hermetically sealed in sterile conditions comprising the liquid pharmaceutical formulation according to claim 1 and appropriate for storage prior to use.

11. A process for the preparation of a liquid pharmaceutical formulation according to claim 9 in which interferon-beta is recombinant and is in a quantity between 0.6 and 1 MIU/ml.

12. A process for the preparation of a liquid pharmaceutical formulation according to claim 11 in which the interferon-beta is 1 MIU/ml, the mannitol is 54.6 mg/ml, and 0.5 mg/ml of albumin in a solution of 0.01 M acetate buffer at pH 3.5 is employed.

13. A container hermetically sealed in sterile conditions comprising the liquid pharmaceutical formulation according to claim 12 and appropriate for storage prior to use.

14. A container hermetically sealed in sterile conditions comprising the liquid pharmaceutical formulation according to claim 11 and appropriate for storage prior to use.

15. A liquid pharmaceutical formulation according to claim 8, in which interferon-beta is recombinant.